PRELIMINARY SAFETY AND EFFICACY OF BGB-11417, A POTENT AND SELECTIVE B-CELL LYMPHOMA 2 (BCL2) INHIBITOR, IN PATIENTS (PTS) WITH ACUTE MYELOID LEUKEMIA (AML)

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Objectives: BCL2, a key regulator of apoptosis promoting cancer cell survival, is aberrantly expressed in many hematologic malignancies. The BCL2 inhibitor, venetoclax, is standard of care for the treatment of newly diagnosed AML in adults unfit for induction chemotherapy. Although venetoclax-based treatments have improved outcomes for pts with AML, there are concerns surrounding disease resistance after continued use and adverse events (AEs) such as gastrointestinal toxicities and neutropenia. Clinical findings have shown that 20-30% of pts using venetoclax are refractory to treatment, and a majority of pts who initially achieve remission ultimately relapse (*N Engl J Med.* 2020;383(7):617-629). The highly selective investigational BCL2 inhibitor, BGB-11417, demonstrated more potent antitumor activity than venetoclax in preclinical studies (*Cancer Res*. 2020;80[suppl, abstr]:3077). To present preliminary safety and efficacy results of BGB-11417 in combination with azacitidine in pts with AML enrolled in BGB-11417-103 (NCT04771130).

Methods: BGB-11417-103 is an ongoing phase 1b/2, global, multicenter, dose-escalation and expansion study evaluating the combination of BGB-11417 and azacitidine in pts with AML (either treatment-naïve [TN] unfit for intensive induction chemotherapy or relapsed/refractory [R/R]), myelodysplastic syndrome, or myelodysplastic syndrome/myeloproliferative neoplasm. Pts who received prior azacitidine or BCL2 inhibitors were excluded. For pts with AML, the 10-day regimen consisted of BGB-11417 at 40 mg (Cohort 1), 80 mg (Cohort 2), or 160 mg (Cohort 3) in combination with azacitidine (75 mg/m^2 x 7 days). In Cycle 1, a 4-day ramp-up of BGB-11417 was utilized starting at 1/8 of the target dose. The window to assess dose-limiting toxicity (DLT) was up to Day 28 for nonhematologic toxicities and Day 42 or initiation of Cycle 2 for hematologic toxicities. Treatment-emergent AEs were graded per Common Terminology Criteria for AEs v5.0. Responses were assessed using the 2017 European LeukemiaNet criteria (*Blood.* 2017;129(4):424-447). All pts gave informed consent.

Results: As of 10 January 2022, 27 pts with AML were treated with the combination therapy (6 in Cohort 1; 15 in Cohort 2; 6 in Cohort 3; Table). Median age was 80 yrs (TN; 18 pts) and 70 yrs (R/R AML; 9 pts); 44% of pts had adverse karyotype. Median prior line of therapy for R/R AML was 1 (range 1-2). At a

median study follow-up of 2.1 months and median duration of treatment of 1.84 months (range 0.3-7.6), 2 of 23 evaluable pts experienced DLTs (Grade 4 neutropenia and Grade 4 thrombocytopenia at the 80 mg x 10 day dose level), which did not meet the safety stopping protocol criteria. Laboratory tumor lysis syndrome (TLS) was observed in 1 pt with a known history of chronic kidney disease treated with 160 mg x 10 day; pt was asymptomatic and TLS resolved within 4 days. Most common nonhematologic AEs were constipation (37%) and azacitidine injection-site reaction (33%). Most common Grade ≥3 hematologic AEs were neutropenia (44%), thrombocytopenia (41%), and anemia (37%). No pts required dose reductions of BGB-11417. Majority (n=17; 63%) of pts are continuing study treatment. Ten pts discontinued due to AEs (n=3), proceeding to transplant (n=3), consent withdrawal (n=2), or disease progression (n=2). Preliminary CR/CRh rates for TN and R/R were 56% and 44%, respectively. Seven of the 9 CRs were achieved by end of Cycle 1.

Conclusions: Preliminary results show that a 10-day regimen of BGB-11417 plus azacitidine resulted in a majority of CR observed by the end of Cycle 1 and was well tolerated in pts with AML.

Table: Baseline Characteristics and Preliminary Efficacy Outcomes

n (%)	40 mg x 10 days		80 mg x 10 days		160 mg x 10 days		Total	
	TN (N=4)	R/R (N=2)	TN (N=10)	R/R (N=5)	TN (N=4)	R/R (N=2)	TN (N=18)	R/R (N=9)
Female	3 (75)	1 (50)	6 (60)	2 (40)	2 (50)	2 (100)	11 (61)	5 (56)
Age yrs, median (range)	82.5 (64-86)	55 (36-74)	77.5 (67-85)	70 (54-78)	82.5 (76-87)	55 (42-68)	80 (64-87)	70 (36-78)
De novo AML	3 (75)	2 (100)	9 (90)	3 (60)	3 (75)	2 (100)	15 (83)	7 (78)
AML risk								
Intermediate	1 (25)	2 (100)	5 (50)	1 (20)	1 (25)	1 (50)	7 (39)	4 (44)
Adverse	3 (75)	0	3 (30)	3 (60)	2 (50)	1 (50)	8 (44)	4 (44)
ORR[*†]	2 (50)	2 (100)	8 (80)	2 (40)	3 (75)	1 (50)	13 (72)	5 (56)
95% CI	(6.76, 93.24)	(15.81, 100.00)	(44.39, 97.48)	(5.27, 85.34)	(19.41, 99.37)	(1.26, 98.74)	(46.52, 90.31)	(21.20, 86.30)
CR	2 (50)	0	5(50)	1 (20)	1 (25)	0	8 (44)	1 (11)
CRi	0	2 (100)	1 (10)	1 (20)	1 (25)	1 (50)	2 (11)	4 (44)
MLFS	0	0	2 (20)	0	0	0	2 (11)	0)
PR	0	0	0	0	1 (25)	0	1 (6)	0
Not done[‡]	1 (25)	0	1 (10)	0	1 (25)	0	3 (17)	0
CRh	0	2 (100)	2 (20)	1 (20)	1 (25)	0	3 (17)	3 (33)
CR or CRh	2 (50)	2 (100)	6 (60)	2 (40)	2 (50)	0	10 (56)	4 (44)
CR or CRi	2 (50)	2 (100)	6 (60)	2 (40)	2 (50)	1 (50)	10 (56)	5 (56)
Time to CR, median (mo)	1.31	N/A	1.31	3.75	0.95	N/A	1.31	3.75

AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery (*Blood Rev*. 2018;32(5):416-425); CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; mo, months; N/A, not applicable; ORR, overall response rate; PR, partial remission; R/R, relapsed/refractory; TN, treatment-naïve; yrs, years.

[*]ORR included CR, CRi, MLFS and PR; [†]Best overall response by investigator; [‡]Response evaluation was not done in 3 pts due to unrelated AE (sepsis, n=2) and consent withdrawn (n=1) in Cycle 1.